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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/500,750	01/03/2005	Yoichi Iimura	0425-1138PUS1	6756

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EXAMINER	
CHANG, CELIA C	
ART UNIT	PAPER NUMBER
1625	

NOTIFICATION DATE	DELIVERY MODE
01/25/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/500,750	IIMURA ET AL.	
	Examiner	Art Unit	
	Celia Chang	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25 and 27* is/are pending in the application.

4a) Of the above claim(s) *1-10,16,17,25 and 27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-14, 18-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election without traverse of group IV, claims 11-15, 18-24 with example 44 as the elected species in the reply filed on Oct. 26, 2007 is acknowledged.

Claims 26 and 28 have been canceled. Claims 1-10, 16-17, 25 and 27 are withdrawn from consideration per 37 CFR 1.142(b).

Claims 11-14, 18-24 are pending.

2. Claims 13-15, 18, 21, 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is unclear what does the term "agent" mean. If the claims are composition and the compound is the single active ingredient, then, such composition must contain a therapeutically effective amount since a pharmaceutical composition cannot be either ineffective or toxic. The term agent does not offer any limitation to the quantitative relationship required by the "pharmaceutical" preamble.

Further, it is ambiguous as to what is the quantity of the required active ingredients embraced by the condition "improving a disease" "improving intellectual function" and both "antagonist" and "agonist". Please note that while a therapeutically effective amount for treating a specific disease such as glaucoma or symptom such as memory loss can be assessed of its dosage and efficacy, there is no measurement of how "improvement" can be ascertained since such term is relative and subjective. In addition, it is unclear how a person's intellectual function can be improved.

Claim 23 is confusing as to how many composition is encompassed by the claim. Is it one composition comprising a quantity therapeutically effective against glaucoma, migraine etc. or is it multiple compositions each containing an anit-myasthenia gravis effective amount, an anti-migraine effective amount etc. Please note that a composition effective for treating glaucoma is topical, a composition for treating attention-deficit hyperactivity disorder is neurological i.e. contains a systemic administration carrier, thus, each composition not only

differ in its dosage for its designated activity but also differ in carrier. The scope of the claim is confusing.

3. Claims 18-24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916), where the Supreme Court looked to whether the experimentation needed to practice an invention was undue or unreasonable. *Id.* An invention must be described so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988). As stated in the MPEP 2164.01(a) "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". The analysis must consider all the evidence related to each of these factors, and any conclusion of nonenablement must be based on the evidence as a whole. *Id.* at 740, *Id.* at 1407. The factors to be considered herein are those set forth as the In re Wands, 8 USPQ 2nd 1400 (1988) decision.

The analysis is applied to the instant case.

Nature of invention

The claims are drawn to compositions containing an active ingredient in an amount effective for *preventing, treating or improving a mental disorder, intellectual function or senile dementia, cerebrovascular dementia.....or migraine.*

The state of the art and predictability

In the strictest sense, the term "preventing" require zero occurrence of a named condition. Such scope, even for vaccine, cannot be achieved. Further, the condition which is considered "improvement" is subjective. The same condition in one person considered an improvement may not be acceptable in another person, thus, no objective measurement can be made as to formulate dosage in a composition as to improve the various mental conditions as named. Further, there is currently no uniform measurement of "intellectual function" which is a cumulative result of genetics, education, environment etc. thus, no single parameter can measure intellectual functionality objectively.

The amount of guidance and working examples

No data or measurement of prevention or improvement or how objective measurement was conducted as to enable one having ordinary skill in the art to make and use such a "composition" as to prevent, treat or improve the above designated mental conditions. On pages 42-45 of the specification IC50 of the compounds were compare with Donepizil in the sigma receptor binding activity and Acetylcholine esterase inhibitory activity. Such in vitro data provided no nexus to the in vivo functionality of such biological receptor or enzyme. Especially, it was described in the specification that such receptor/enzyme function can be sometimes agonistic and other times antagonistic which result in completely different physiological functionality for the receptor/enzyme. Absent of specific and objective measurement such as Becker et al. or Waters with clinical trial, one having ordinary skill is offered mere screening for further testing rather than enablement of the compounds.

4. Claims 11-12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The scope of the claims encompassing "hydrate" lacks sufficient description and enablement. Unlike pharmaceutically acceptable addition salts which are formed after the compounds are made and conventional process of salt formation using a conventional pharmaceutically acceptable acid or base; hydrates (a specific solvate) are considered a separate chemical entity which chemical identity is different from the compound per se (see Seddon). It is also well recognized in the art that there is absolutely no predictability of which compound can or cannot form hydrates because there is no routine process for such prediction (see Braga et al. p.3640 right column). The specification provided no compound which will form a hydrate. Since such product, as evidenced by the prior art, can only be supported when one is in possession of a hydrate, the absence of any hydrate for the claimed compound cannot support such a scope of the claims.

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 11-15, 18-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sugimoto et al. US 4,895,841 supplemented with CA110:173102 structural delineation with registry numbers; in view of Iimura et al. US 6,677,330 supplemented with CA 133:207817 structural delineation with registry numbers; further in view of Kato et al. (recited on 1449); or Iimura '330 in view of Sugimoto et al. '841 further in view of Kato et al.

Determination of the scope and content of the prior art (MPEP §2141.01)

Sugimoto et al. '841 or Iimura '330 disclosed acetylcholine esterase inhibitors structurally encompassed the instant claims (see both reference in their entirety). The examples with the structural delineation are provided by CAS for applicants convenience.

Ascertainment of the difference between the prior art and the claims (MPEP §2141.02)

The difference between the instant claims and the examples of the prior art is that the specific substitutents among the instantly claimed compounds are mere picking and choosing among the variations of the generically disclosed Markush elements of Sugimoto and Iimura, and the claimed compositions are sigma receptor binding instead of AcCh esterase inhibiting for treating the same disorder of the prior art.

Picking and choosing among the conventional variation as generically disclosed by the prior art is prima facie obvious in absence of unexpected results. In re Lemin 141 USPQ 814. Especially, the instant compounds are well exemplified by the prior art for example:

Claim 11. Compound 13, see RN120013-58-3 vs RN 120013-98-1;
Compound 27, see RN 120013-63-0 vs RN 290309-08-9;
Compound 28, see RN 290308-81-6 vs RN 290308-85-9;
Compound 29, see RN 290309-10-3 vs RN 290308-85-9;
Compound 30, see RN 209309-12-5 vs RN 290308-85-9;
Compound 34, see RN 290308-79-1 vs RN 290308-85-9; etc.

This is not an exhausted listing. However, the specific examples in combination with the generic disclosure rendered the instant claims which differ in chain length of the alkoxy moieties, substituents on the benzyl ring, or asymmetric substitution in the indenonyl ring prima facie obvious picking and choosing.

Further, Kato et al. taught that the indenolyl-piperidine compounds known to have AcCh-esterase activity would be expected to have similar sigma receptor binding activity.

Finding of prima facie obviousness—rational and motivation (MPEP§2142-2143)

One having ordinary skill in the art in possession of the above references would be in possession of the instantly claimed compounds and their compositions because one has been given the options of alternative substituents on the indaonyl-piperidinyl core with ample of operable examples to guide one skilled in the art to expect combination of all the variables in the prior art is expected to have similar activity. The teaching, suggestion and expectation by the prior art would motivate one skilled in the field to prepare and use the instant claims for the same utility. Absent of unexpected result, there is nothing unobvious in picking some among many. In re Lemin 141 USPQ 814.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celia Chang, Ph. D. whose telephone number is 571-272-0679. The examiner can normally be reached on Monday through Thursday from 8:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet L. Andres, Ph. D., can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

OACS/Chang
Jan. 19, 2008

Celia Chang
Primary Examiner
Art Unit 1625